RECEIVED
CENTRAL FAX CENTER
OCT 1 1 2007

REMARKS

Claims 1-11 and 20-27 are pending in the present application. Claims 1 and 11 were amended to emphasize the computational nature of claimed invention. These claims were also amended to address "minor informalities." All pending claims have been rejected. The rejections are traversed for the reasons set forth below.

The amendments to claim 1 find support throughout the specification; see e.g., paragraph [0146]. New independent claim 20 finds support at, *inter alia*, original claims 1, 10 and 11. New independent claim 24 recites features that discussed at paragraphs [0035], [0062], [0117], and [0127], for example. New dependent claims 21-23 and 24-27 find support at in original claims 2-4, for example.

Objection to Claims – Minor Informalities

The Examiner objects to the word "extract" in claims 1, 2, and 11, suggesting that the term might be interpreted in a chemical context (treating one material with another to take out some material from the material being treated). However, from the context of the claim and the specification, it should be clear that the word "extract" in the claims refers to a computational operation. The amendment to claim 1 makes this even more clear: "the analysis computationally extracts data from the image . . . ." Withdrawal of the objection is respectfully requested.

Next, the Examiner objected to claims 1(b) and 11 because of an allegedly improper recitation Markush groups. Applicants have overcome this objection by amending the claims to use the traditional language for a Markush group.

Next, the Examiner objects claim 2 for seeming to be grammatically incorrect: "in Claim 2 at line one after the word 'claim' the ',' (i.e., comma) seems to be grammatically incorrect." Applicants do not understand objection. Claim 2 does not contain a comma after the word "claim," so the objection seems misplaced.

The Examiner also objects to claim 6 for the recitation "support cells." According the Examiner this "'support cells' is unclear because it is not clear in what way those cells are supporting hepatocytes." The term "support cells" is well understood in the art and no further clarification is deemed necessary. The term generally means cells that "support" in a physical and/or chemical way primary cells such as hepatocytes. See for example paragraph [0070] of the instant specification which reads as follows:

> In some embodiments, hepatocytes can be cultured with associated cells to encourage the hepatocytes to behave naturally in an assay. For instance, hepatocytes can be co-cultured with stromal cells such as fibroblasts. Co-culturing hepatocytes and support cells in this manner may improve the predictive qualities of the assays in some contexts.

The meaning is made abundantly clear in US Patent No. 6,599,694, which is incorporated by reference in the present specification. In that patent, support cells are further exemplified:

> Stromal cells are supporting cells that are mesenchymal in origin. Examples of stromal cells include fibroblasts of the connective tissue, blood elements such as macrophages, and nervous system supporting cells such as oligodendricytes and Schwann cells.

In view of the well understood meaning of "support cells," no amendment to claim 6 is deemed necessary. Withdrawal of the objection is respectfully requested.

Lastly, claims 8-9 were objected to for using the term "immortalized," which was said to be unclear. The Examiner questions whether this recitation is similar to what is known in the art for describing "HeLa cell lines."

It is respectfully submitted that the term *immortalized* is clear and definite in the context of the claims. One type immortalized hepatocyte referenced in the present specification is the HepG2 cell line identified at paragraph [0065]. A further detailed discussion of immortalized hepatocytes is presented at the paragraphs following paragraph [0065], e.g., paragraphs [0066]-[0068].

In view of the well understood meaning of "immortalized" as it refers to hepatocytes, withdrawal of the objection to claims 8-9 is respectfully requested.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner presents two rejections based on insufficient antecedent basis. Applicants do not understand either rejection because the terms allegedly lacking antecedent basis do not use the definite article "the" or "said." As such, there is no antecedent basis issue. MPEP 706.03(d) and MPEP 2173.05(e)

First, the Examiner points to the language "hepatocyte culture" at Claim 2, line 2. However claim 2 recites "*a* hepatocyte culture." Because the claim does not recite "*the* hepatocyte culture," the claim language does not present an improper antecedent basis problem. Withdrawal of the rejection is respectfully requested.

Second, the Examiner rejects claim 6 for using the phrase "hepatocytes are co-cultured with support cells." The Examiner notes that

> Claim 6 depends from Claim 3. Claim 3 recites, "multiple hepatocyte cultures are located on a single support structure . . ." There is no mention of co-culturing hepatocytes in Claim 3. Appropriate correction is required.

There would be a problem if claim 6 contained the wording "the co-culture" or "the co-culturing." However, the claim does not use a definite article with "co-culture" because co-culturing is a new claim feature first introduced in claim 6. Therefore there is no antecedent basis problem, and it is respectfully submitted that the rejection should be withdrawn.

Claim Rejections Under 35 U.S.C. §102

Claims 1, 7, and 10-11 were rejected under 35 U.S.C. 102(b) as anticipated by an article of Aljajeh et al. (Indian Childhood Cirrhosis-Like Liver Disease in an Arab Child, A Brief Report. 1994. Virchows Archive, Vol. 424, pp. 225-227).

According to the Office,

> Regarding Claims 1, 7 and 10-11, Aljajeh et al. teach methods to a chemical mediated stimulus hepatotoxicities, viz. cholestasis, fibrosis and necrosis in photo and micrographs obtained from photo and electron micrographic observation on hepatocytes in liver tissue of a patient. Said assessment, based on observed changes in hepatocyte organelle structure (e.g., cellular membrane and endoplasmic reticulum) demonstrated diagnosis of cholestasis, fibrosis and necrosis in photo and electron micrographs respectively (See, e.g., legend of Figure 2, Lines 3 and 5 and Abstract). Said necrosis and fibrosis (i.e., hepatotoxicities) were manifestations of effect of higher hepatic copper concentration (See, Page 727, Column 1, Lines 12-23). Photo and electron micrographs, inherently are images of the hepatocytes as observed in a photo, or an electron microscope. Aljajeh et al. also

> mention that hepatic copper concentrations were high in said patient. Clearly the abnormal hepatocyte morphology observed was because of said stimulus, which is inherently a chemical stimulus. Also, please note that Aljajeh et al. describe ≥ 1 hepatotoxic pathologies based ≥ 1 hepatocyte features (i.e., membrane and endoplasmic reticulum morphologies). Therefore, the prior art method clearly anticipates Applicants' claimed invention in Claims 1, 7 and 10-11. (Page 4 of April 11, 2007 Office Action).

Applicants take issue with various aspects of this rejection. For example, original claim 1 recited "classifying the stimulus by *quantitatively* evaluating the extracted features to identify one or more hepatotoxic pathologies resulting from the stimulus . . . ." The Aljajeh et al. reference contains no suggestion of a quantitative technique for evaluating extracted features.

In addition, claim 1 recites

> (a) analyzing an image of hepatocytes that have been exposed to a *stimulus* . . .; and
>
> (b) classifying the *stimulus* . . . to identify one or more hepatotoxic pathologies resulting from the *stimulus* . . . .

According to the Office, high hepatic copper concentrations identified in the Aljajeh et al. article qualify as a *stimulus* within the meaning of the claim. However it is not clear from the article whether the high copper concentrations are a cause or an effect of the observed hepatocyte pathology. Even if it is in fact a cause of the observed pathology, the article does suggest that the authors *classified* the high copper concentration in any manner, and certainly not "to identify one or more hepatotoxic pathologies resulting from the stimulus".

Fundamentally, the claimed invention is a quantitative, computational technique. While Applicants believe that this is implicit in the language of the originally submitted method claims, the claims have been amended to emphasize the computational aspect of the invention. Specifically, claim 1 now explicitly recites the use of a *computational* device, an analysis that *computationally* extracts data from the image, etc.

The Aljajeh et al. article does not suggest a computational method as recited in claim 1:

> (a) analyzing, *with a computational device*, an image of hepatocytes that have been exposed to a stimulus, wherein the analysis *computationally extracts data from the image, which data represents* features characterizing the hepatocytes; and

> (b) classifying, *with the computational device*, the stimulus by quantitatively evaluating the extracted data which represents features to identify one or more hepatotoxic pathologies resulting from the stimulus, wherein *the computational device is configured to classify* at least two hepatotoxic pathologies selected from the group consisting of necrosis, cholestasis, steatosis, fibrosis, apoptosis, and cirrhosis.

Nor does the Aljejeh et al. article suggest a computational device

> configured to classify at least two hepatotoxic pathologies selected from the group consisting of necrosis, cholestasis, steatosis, fibrosis, apoptosis, and cirrhosis.

Because the Aljejeh et al. article does not suggest using a computation device or a computational process of the types claimed, it is respectfully submitted that claims are not anticipated by the article. Withdrawal of the §102 rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §103(a)

Claims 1-11 were rejected under 35 U.S.C. §103(a) as obvious over combined teachings of the Aljajeh et al. article in view of *Powers et al.* (A Microfabricated Array Bioreactor for Perfused 3D Liver Culture. 2002. Biotechnology & Bioengineering, Volume 78, pp. 257-269), *Le Cluyse et al.* (Expression and Regulation of Cytochrome P450 Enzymes . . . . J. Biochem Molecular Toxicology. 2000. Volume 4, Number 4, pp. 177-188), and, in the case of claims 8-9, *Morel et al.* (1990, Expression of Cytochrome P-450 enzymes in Cultured Human Hepatocytes, Eur. J. Biochem., Volume 191, pp. 437-444).

As explained, the Aljajeh et al. article fails to suggest a computational method employing the computational operations recited in claim 1 (or in the newly submitted independent claims, claims 20 and 24). The three additional references cited in the section 103 rejection fail to provide the claimed computation aspects that are missing in the Aljajeh et al. article.

First, the Powers et al. article describes a bioreactor shown to support a culture of rat hepatocytes. The reactor was used for *in situ* imaging of the hepatocytes using two-photon microscopy. Further, fluorescence levels in the images were used monitor expression levels of a gene for EGFP. However, the article contains no suggestion that the images should be analyzed in a manner that "computationally extracts data from the image, which data represents features characterizing the hepatocytes" and is used in "classifying . . . the stimulus by quantitatively evaluating the extracted . . . features to identify one or more hepatotoxic pathologies resulting from the stimulus."

RECEIVED
CENTRAL FAX CENTER

OCT 1 1 2007

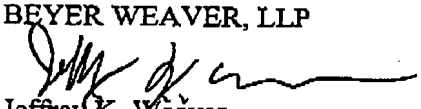
The next reference, the *Le Cluyse et al.* article describes a study of inducibility of cytochrome P450 enzymes in cultures of human hepatocytes. While SEM images of the hepatocytes were taken, it does not appear that the authors considered computationally extracting data from an image or quantitatively evaluating extracted data to identify one or more heptotoxic pathologies. The *Morel et al.* article similarly describes a study of inducibility of cytochrome P450 enzymes and like the Le Cluyse et al. article fails to suggest computationally extracting or quantitatively evaluating data from an image.

In view of the above, it is respectfully submitted that the claimed invention is patentable over the four cited references. Withdrawal of the §103 rejections is respectfully requested.

Conclusion

Applicants believe that all pending claims are allowable and respectfully request a Notice of Allowance for this application from the Examiner. Should the Examiner believe that a telephone conference would expedite the prosecution of this application the undersigned can be reached at the telephone number set out below.

Respectfully submitted,
BEYER WEAVER, LLP



Jeffrey K. Weaver
Reg. No. 31,314

P.O. Box 70250
Oakland, CA 94612-0250
(510) 663-1100